Continuously stable strategy of pathogen evolution in a classic epidemiological SIR model

Han Xiao-zhuo[1], Hui Cang[2,3], Li Feng[1], Lin Meng-xing[1]

1. School of Applied Mathematics, Guangdong University of Technology, Guangzhou 510520, China
2. Centre for Invasion Biology, Department of Mathematical Sciences, University of Stellenbosch, Matieland 7602, South Africa
3. Mathematical and Physical Biosciences, African Institute for Mathematical Sciences, Muizenberg 7945, South Africa

Abstract: Using the framework of adaptive dynamics, here a classic susceptible-infected-recovery (SIR) host-pathogen model was considered to explore the evolutionary dynamics of pathogen virulence. Both transmission rate and recovery rate were assumed to be constrained by trade-offs with the pathogenic virulence, and the trade-offs crucially determined the behavior of the evolutionary dynamics. No additional increase in mortality due to infection was assumed and the invasion fitness and evolutionary trajectories of pathogen virulence were explored using pairwise invadability plots. The results showed that initial strains of viruses with different levels of virulence converged to one continuously stable singular point, prohibiting any other complex evolutionary outcomes to occur on the strain diversity. The insufficient nonlinearity in the population dynamics and the lack of additional increase of mortality due to infection could have led to the lack of evolutionary diversity, which could, nonetheless, serve as the base for developing potential mechanisms for reducing the diversity of virus strains in public health management.

Keywords: host-pathogen; adaptive dynamics; continuously stable strategy; evolutionary path; virulence management

CLC number: Q141 **Document code:** A **Articlcal ID:** 0455-2059(2018)04-0517-08

DOI: 10.13885/j.issn.0455-2059.2018.04.013

经典流行病学SIR模型中病原进化的连续稳定对策

韩晓卓[1], 惠　苍[2,3], 李　锋[1], 林梦醒[1]

1. 广东工业大学 应用数学学院, 广州 510520
2. 斯坦林布什大学 数学科学系 南非入侵生物学杰出研究中心, 马铁兰德 7602, 南非
3. 非洲数学科学研究机构 数学与理论物理生物学, 梅森堡 7945, 南非

摘　要：基于经典传染病学中的易感–感染–恢复的寄主与病原体关系模型, 利用适应性进化动态的理论框架, 研究病原体毒性的进化动态. 模型假设疾病的传染率和恢复率均受到来自于病原体毒性的妥协关系的限制, 这种妥协关系是决定进化动态的关键因素. 为了分析简单, 模型除寄主自身固有死亡率外, 并没有假设由疾病感染引起的额外致死率, 通过分析PIP图中入侵适合度的变化和病原毒性的进化

Received date：2018-04-27

Found term：Supported by the National Natural Science Foundation of China (31670391) and South African National Research Foundation(No89967)

Biography：Han Xiao-zhuo (1978−), female, born in Xining, Qinghai Province, associate professor, doctor, mast supervisor, e-mail: hanxzh@gdut.edu.cn, majoring in mathematical ecology;
Li Feng (1977−), male, born in Jining, Shandong Province, lecturer, master supervisor, e-mail: lfsecurity@gdut.edu.cn, majoring in biomathematics and cryptology, corresponding author.

轨迹. 结果表明: 在该系统中, 具有不同毒性水平的初始病株最终都将收敛到同一个连续的稳定奇点, 并抑制了毒株多样性的其他复杂进化结果的发生. 种群动态中非线性关系的不充分性和额外病毒致死率的缺失是导致毒性进化多样性缺乏的主要原因. 结果将为公共健康管理事业中如何减少病原毒株的多样性提供可行的潜在性机制.

关键词： 寄主–病毒; 适应性动态; 连续稳定对策; 进化路径; 毒性管理

Epidemiology forms a core discipline of research for human health, and also the health of domestic plants and animals, with emerging infectious diseases posing a continuous threat to public health. A short generation time and high mutation rate allow pathogens to evolve rapidly. It is therefore essential to incorporate evolutionary dynamics of pathogens in health management planning[1−2]. However, it was only in the 1970s that evolutionary game theory eventually extended its framework to incorporate frequency-or density-dependent selection.

Adaptive dynamics (AD) extends the evolutionary game theory by describing the dynamics of adaptive traits and analyzing the evolutionary implications of complex ecological setting[3−5]. AD studies evolutionary changes induced by rare and small mutations when fitness is density or frequency dependent[6]. As individuals interact with each other within a community, their fitness not only depends on their own traits but also the frequency or density of traits of conspecific and other species. The evolution of traits can be evaluated by examining the invasion of rare mutants in a community dominated by resident populations sitting at their stable equilibriums. During the past 20 years, an increasingly large number of research groups have utilized the AD method to explore the evolutionary dynamics of host-pathogen systems[7−16].

Here we consider a classic susceptible-infected-recovery (SIR) host- pathogen model and explore the evolutionary dynamics of pathogen virulence using the AD framework. Comparing with other models of virulence evolution[2], our model does not consider any additional increase in mortality due to infection. We assume that both transmission rate and recovery rate are under particular trade-offs with the virulence of pathogens, and it have been suggested in a number of publications that the evolutionary outcomes may strongly depend on the shape of the trade-off function[12−14, 17−19]. We present our results in the form of, pairwise invasion plots and the evolutionary trajectory of pathogen virulence. These portraits show a continuously stable strategy of a singular point without evolutionary branching or diversification. We, hence, discuss the potential as to how we can reduce strain diversity of viruses in public health management.

1 Model

Two different time scales need to be distinguished in the AD framework: a slow evolutionary time scale (including a slow trait shift by directional selection and an even slower evolutionary branching by disruptive selection) and a fast- ecological time scale. In this regard, we illustrate here the standard procedure of using AD in an epidemiological SIR model.

1.1 SIR population dynamics (ecological time scale)

The ecological assumptions made below are needed simply to specify a dynamical system and can be altered to match the behavior of particular ecological realism. The basic host- pathogen model was considered based on Anderson et al[1]:

$$\begin{cases} \dfrac{\mathrm{d}S}{\mathrm{d}t} = bN - \beta SI - dS, \\ \dfrac{\mathrm{d}I}{\mathrm{d}t} = \beta SI - \theta I - dI, \\ \dfrac{\mathrm{d}R}{\mathrm{d}t} = \theta I - dR. \end{cases} \tag{1}$$

Where N is the total population size, S the number of susceptible individuals, I the number of infected individuals and R the number of recovered and immunized individuals. Parameters b and d are, respectively, the birth rate and the death rate of individuals. When they are constants, the transmission rate

β and the recovery rate θ will decide the dynamics of the system. Here we assume that no additional mortality is caused by the pathogenic disease.

1.2 Virulence dynamics (evolutionary time scale)

Adaptive dynamics was used to discuss the evolutionary consequence of the pathogenic disease. Let trait x be the virulence of the pathogen. The transmission rate β and the recovery rate θ are affected by this trait. Based on Best et al's[16] model (also see [20−21]), we consider the transmission rate as the following:

$$\beta(x)=\frac{\varepsilon}{1+e^{-k(x-x_0)}}. \tag{2}$$

This is an increasing function with virulence traits, meaning greater trait values will have a higher transmission rate. The parameter ε sets the upper bound for the transmission rate. The parameter k measures the sensitivity of transmission rate to the level of virulence. x_0 is a constant to shape the curve, and we let $x_0=0.5$ in the following without losing generality.

Host defense to pathogenic diseases may be achieved through avoidance (lowered susceptibility), clearance (increased recovery), or tolerance (lowered pathogen-induce mortality)[22]. Since there is no pathogen-induced mortality in our system, for simplicity, we only consider the clearance rate of infections. A primary proposition is that host's recovery rate increases with virulence[23], which could be described as the following:

$$\theta(x)=\frac{\alpha x}{x+c}, \tag{3}$$

where parameters α and c depict the saturation level and the camber of the curve, respectively. Combining the equations (1), (2) and (3), the evolutionary dynamics of pathogens in host environments can be analyzed.

Let $x'=x+\delta_x$ be the trait value of a rare mutant, with x and δ_x representing the resident trait and the magnitude of mutant per unit time. $\hat{S}$ and $\hat{I}$ are the population sizes of susceptible (S) and infected (I) individuals at equilibrium. Then the invasion fitness of virulence mutant was deduced in terms of AD framework:

$$\varphi(x',x)=\beta(x')\hat{S}-\theta(x')-d=\frac{\varepsilon\hat{S}(x)}{1+e^{-k(x'-x_0)}}-\frac{\alpha x'}{x'+c}-d. \tag{4}$$

The selection gradient of infectious population, measuring the sensitivity of the mutant's initial rate of increase to changes in its phenotype:

$$g(x)=\left.\frac{\partial\varphi(x',x)}{\partial x'}\right|_{x'=x}=\left.k\varepsilon\hat{S}(x)\frac{e^{-k(x'-x_0)}}{\left(1+e^{-k(x'-x_0)}\right)^2}-\frac{\alpha c}{(x'+c)^2}\right|_{x'=x}, \tag{5}$$

determines the speed of directional selection.

1.3 Pathogen's evolutionary trajectory

The evolutionary dynamics of the virulence x can be depicted by two ways. One is the canonical equation, which is proportional to the selection gradient[24]:

$$\dot{x}=\frac{1}{2}\mu\sigma^2\hat{I}(x)\left.\frac{\partial\varphi(x',x)}{\partial x'}\right|_{x'=x}, \tag{6}$$

where μ and σ^2 are parameters related to the rate and variation of mutational steps. $\hat{I}(x)$ is the population sizes of infected (I) individuals at equilibrium. The term $\frac{1}{2}\mu\sigma^2\hat{I}(x)$ scales the rate of evolution, and the selection fitness, $\left.\frac{\partial\varphi(x',x)}{\partial x'}\right|_{x'=x}$, carries all the information about trait dynamics.

The other way is to envisage the sequential trait substitution as a stochastic representation of the mutation-selection process in term of the master equation (see details in [5]). The transition probability per unit time for the trait substitution from x to x', $w(x',x)$, is decided by the following:

$$w(x',x)=\mu\cdot b\cdot\hat{I}(x)\cdot M(x'-x)\cdot b^{-1}(x',x)\cdot\left(\varphi(x',x)\right)_+, \tag{7}$$

where parameters μ and b denote the fraction of birth leading to mutation and the per capita birth rate in the infected individuals. The probability of a mutation occurring, $M(x'-x)$, obeys the distribution function. Hence, the term $\mu\cdot b\cdot\hat{I}(x)\cdot M(x'-x)$ represents the probability that the mutant enters the population. Here, $b^{-1}(x',x)=1/b(x',x)$. The function

$\left(\varphi(x', x)\right)_+$ keeps positive values of fitness unchanged and maps negative ones to zero. The term $b^{-1}(x', x) \cdot \left(\varphi(x', x)\right)_+$ represents that the mutation successfully escapes accidental extinction, reflecting the selection process.

When the selection gradient of resident trait disappears, termed an evolutionary singularity (x^*), we need to further analyze the second derivative (curvature) of invasion fitness to judge whether the evolution ceases or continues at this point. The singularity is evolutionarily stable (i.e. ESS) if the fitness reaches a maximum[24], in this case,

$$\left.\frac{\partial^2\varphi(x', x)}{\partial x'^2}\right|_{x'=x^*} < 0. \tag{8}$$

A fitness minimum, conversely, represents the trait to be an evolutionarily unstable, where evolutionary branching may occur. The two necessary and sufficient branching conditions at x^* are:

$$\left.\frac{\partial^2\varphi(x', x^*)}{\partial x'^2}\right|_{x'=x^*} > 0 \ \& \ \left.\frac{\partial^2\varphi(x', x)}{\partial x\partial x'}\right|_{x'=x=x^*} < 0. \tag{9}$$

There are other situations if various conditions are satisfied. For instance, the condition:

$$\left.\frac{\partial^2\varphi(x', x^*)}{\partial x'^2}\right|_{x'=x^*} + \left.\frac{\partial^2\varphi(x', x)}{\partial x\partial x'}\right|_{x'=x=x^*} < 0. \tag{10}$$

means that the singularity is convergence- stable. When a fitness maximum (i.e. an ESS) is convergence-stable (i.e. a CSS) but the dimorphism cannot be protected, it is called an evolutionary trap[25]. If the directional selection pushes the trait to become unfeasible (i.e. the population size at equilibrium become equal to or less than 0), it is termed an evolutionary suicide[26].

Due to the difficulty in deriving analytic solution for complex systems, numerical analysis and/or individual- based model are often used to explore the evolutionary dynamics. Here, we sought the solutions both analytically and numerically with the parameters that represent population dynamics set at $b=d=2$ and $N=10\ 000$; while those in evolutionary dynamics at $\mu=0.000\ 1$, $\sigma^2=0.001$, $\delta_x=0.000\ 1$.

2 Results

We derived the evolutionary singularity $x^*=0.973\ 2$ obtained from setting Eq.(1) to be zero and Eq.(5) $g(x^*)=0$. We then calculated the second derivative (curvature) of invasion fitness at this point:

$$\left.\frac{\partial^2\varphi(x', x)}{\partial x'^2}\right|_{x'=x^*} = -7.849\ 6,$$

which means the trait value x^* is an ESS. In the monomorphic case, moreover, the condition,

$$\left.\frac{\mathrm{d}g(x)}{\mathrm{d}x}\right|_{x=x^*} < 0,$$

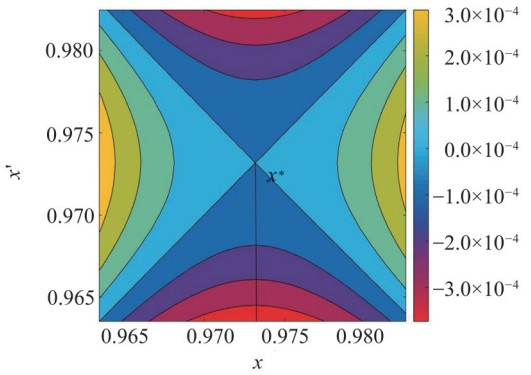
guarantees the eigenvalue of the trait dynamics to be negative:

$$\left.\frac{\mathrm{d}(\dot{x})}{\mathrm{d}x}\right|_{x=x^*} = \left.\frac{\mathrm{d}}{\mathrm{d}x}\left(\frac{1}{2}\mu\sigma^2\hat{I}(x)\frac{\partial\varphi(x', x)}{\partial x'}\right)\right|_{x'=x=x^*} =$$

$$\left.\frac{1}{2}\mu\sigma^2\hat{I}(x)\frac{\mathrm{d}g(x)}{\mathrm{d}x}\right|_{x=x^*} < 0,$$

meaning that the evolutionary dynamics converge to such a singular point. Therefore, this evolutionary singularity x^* is also a continuously stable strategy (CSS).

The evolution of a monomorphic population can also be analyzed by means of a pairwise invadability plot (PIP). It is essentially a plot of the initial per capita rate of increase of mutation as a function of the mutant trait (x') value and resident trait (x) value, which intersects through the saddle at $\varphi(x', x)=0$ and divides up the area into two sections where the mutation can invade ($\varphi(x', x)>0$) and where it cannot ($\varphi(x', x)<0$) (shown in Fig. 1). The intersection of the diagonal with another line on which $\varphi(x', x)=0$ corresponds to the evolutionary singular strategy x^*. Choose the interval of x and x' to change between (−0.03, +0.03) around the x^*. In

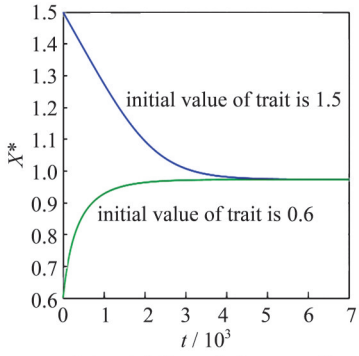


$\varepsilon=0.01$, $k=5$, $x_0=0.5$, $\alpha=10$, $c=2$

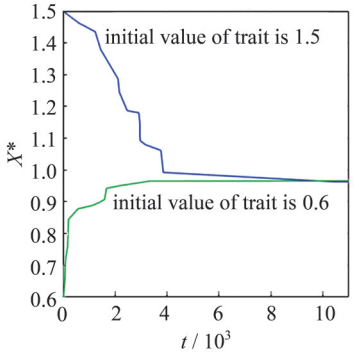
Fig. 1 Pairwise invadability plot of the invasion fitness

terms of the plus-minus sign of invasion fitness, the trait substitution sequence is approximated by a monomorphic evolution along the diagonal, eventually converging to the singular strategy x^*.

The evolutionary outcomes analyzed above can also be proved by portraying the evolutionary trajectory of the trait. Both deterministic and stochastic evolutionary dynamics of the virulence, starting from different initial values of the trait, converged to the singular strategy x^*. As shown in Fig. 2, both the deterministic and stochastic simulations converged quite rapidly. Interestingly, the convergence rate is slower to the singular point x^* when approached from the above (with the initial value of trait being 1.5) than from below (0.6) in both evolutionary trajectories, due to the slight asymmetry in the invasion fitness around x^* (Fig. 1). It should be noted especially that the stochastic results are the mean trait values from the phenotype distributions. Since the stochasticity of mutation and selection processes, that is, the time elapses of the two paths reaching the singular point, were far greater than the time elapses of the deterministic dynamics.



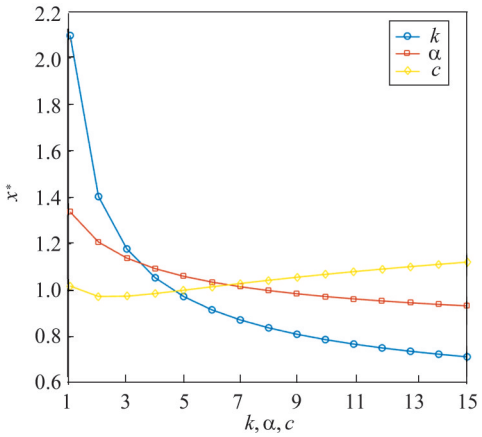
a deterministic evolutionary path



b stochastic evolutionary path

Fig. 2 Evolutionary trajectories from deterministic and stochastic simulations of pathogen virulence

We further explored the effects of changing three parameters in the invasion fitness on the evolutionary dynamics, including parameters k, α and c in the transmission rate and the recovery rate. Changing each parameter from 1 to 15 while fixing the other two parameters, as illuminated in Fig. 3, no bifurcations or evolutionary branching were observed, with only the shifting value of the singular point. The singular point of the trait declined exponentially with increasing parameters k and α, while increased linearly as the parameter c increased. In fact, these results could be expected by analyzing the invasion fitness.



basic values are k=5, α=10, c=2

Fig. 3 Parameter sensitivity of evolutionary singular point to three parameters k, α and c in the transmission rate and the recovery rate on evolutionary dynamics

3 Conclusions

We studied the evolutionary dynamics of pathogens based on the classic SIR model using the framework of adaptive dynamics. Under the specified transmission and recovery rate functions, a conclusion can be drawn that the virulence of such pathogens, even if initially having different levels of virulence, will converge to a stable singular point. This is true regardless of using deterministic or stochastic evolutionary formulations. The system did not induce any complex evolutionary dynamics, such as evolutionary branching, bi-stability or Red Queen dynamics. Such lack of evolutionary complexity is in general due to the absence of strong nonlinear incidence functions of population dynamics[20, 27–30].

Theoretically, the evolution of virulence depends on the impacts of alternative transmission modes and ecological feedbacks, such as the host population structure, competition and predation of pathogens within a host, or host-pathogen coevolution and multilevel selection[2, 31−32]. de Leo et al. stressed that both micro- and macro-parasites can exert strong selection pressures on the host and the frequency-dependent selection plays an important role in the evolution of virulence[33]. Mechanisms to maintain virulence diversity have been well explored based on direct transmitted pathogens. Generally, multiply habitats of host[34−36], different vaccination statuses of hosts[22] and different levels of evolved resistance[16] could all lead to the evolution of pathogen in-host diversity. Besides these causes of heterogeneity, the trade-offs between pathogen transmissibility, recovery, pathogen-induced death rate and virulence are also important routes towards strain diversification[29], which are all essential for formulating the fitness function. Great nonlinearity begets complex evolutionary trajectories[37−43]. The nonlinear incidence functions and environmental transmission modes of pathogen, as well as the ecological dynamics of the host-pathogen system, play an important role in shaping the process of pathogen evolution[29]. As suggested here, the use of the simplest assumption of mass action incidence and direct transmissibility function makes it insufficient to trigger evolutionary diversification of virulence in our model.

For virulence management, it is important to elucidate what conditions could trigger a continuously stable virulence into an evolutionary branching or evolving into a strain with a much higher of virulence[9, 18]. To this end, it is crucial for efficient management to understand which factors can reduce the virulence or suppress virulence diversification in wild populations. Mounting evidence is pointing at the conclusion that the transmission modes, the spatial or social structure, the functional trade-offs between the host-pathogen, the infection routes and ecological settings, are all potential sources to affect the evolutionary dynamics of virulence[19, 44]. Regarding our results on the continuously stable strategy, increasing the sensitivity of the transmission rate to virulence (k) or the strength of trade-off between recovery and virulence (α) would benefit the reduction of pathogenic virulence (Fig. 3). Decisions on virulence management are always, thus, fraught with dilemmas, due to the possible conflicts of interest between the individual host and the host population as a whole[45]. Health care practitioners may be confronted with the dilemma of inducing common-but-mild versus rare-but-serious diseases[9].

Acknowledgements: We wish to thank Prof. Richard Law of University of York for discussion and comments. We are grateful to Beverley Laniewski for her constructive comments on this manuscript. Han Xiao-zhuo also thanks the China Scholarship Council and York Centre for complex systems analysis of University of York for its hospitality.

References

[1] Anderson R M, May R M. Infectious diseases of humans: dynamics and control[M]. Oxford: Oxford University Press, 1991.

[2] Dieckmann U. Adaptive dynamics of pathogen-host interactions[C]//Dieckmann D, Metz J A, Sabelis M W, et al. Adaptive dynamics of infectious diseases: in pursuit of virulence management. Cambridge: Cambridge University Press, 2002: 39-59.

[3] Nowak M A, Sigmund K. The evolution of stochastic strategies in the prisoner's dilemma[J]. Acta Applicandae Mathematicae, 1990, 20(3): 247-265.

[4] Metz J A J, Nisbet R M, Geritz S A H. How should we define fitness for general ecological scenarios?[J]. Trends in Ecology and Evolution, 1992, 7(6): 198-202.

[5] Dieckmann U, Law R. The dynamical theory of coevolution: a derivative from stochastic ecological processes[J]. Journal of Mathematical Biology, 1996, 34(5/6): 579-612.

[6] Waxman D, Gavrilets S. 20 questions on adaptive dynamics[J]. Journal of Evolutionary Biology, 2005, 18(5): 1139-1154.

[7] Baalen M V. Coevolution of recovery ability and virulence[J]. Proceedings of the Royal Society B: Biological Sciences, 1998, 265(1393): 317-325.

[8] Day T. On the evolution of virulence and the relationship between various measures of mortality[J]. Proceedings of the Royal Society B: Biological Sciences, 2002, 269 (1498): 1317-1323.

[9] Dieckmann U, Metz J A J, Sabelis M W, et al. Adaptive

dynamics of infectious diseases: in pursuit of virulence management[M]. Cambridge: Cambridge University Press, 2002.

[10] Ganusov V, Bergstrom C, Antia R. Within-host population dynamics and the evolution of microparasites in a heterogeneous host population[J]. Evolution, 2002, 56(2): 213-223.

[11] Day T, Proulx S R. A general theory for the evolutionary dynamics of virulence[J]. American Naturalist, 2004, 163(4): 40-63.

[12] de Mazancourt C, Dieckmann U. Trade-off geometries and frequency-dependent selection[J]. American Naturalist, 2004, 164(6): 765-778.

[13] Kisdi E. Trade-off geometries and the adaptive dynamics of two co-evolving species[J]. Evolutionary Ecology Research, 2006, 8(6): 959-973.

[14] Hoyle A, Bowers R G, White A, et al. The influence of trade-off shape on evolutionary behaviour in classical ecological scenarios[J]. Journal of Theoretical Biology, 2008, 250(3): 498-511.

[15] Best A, White A, Boots M. The implications of coevolutionary dynamics to host-parasite interactions[J]. American Naturalist, 2009, 173(6): 779-791.

[16] Best A, White A, Kisdi E, et al. The evolution of host-parasite range[J]. American Naturalist, 2010, 176(1): 63-71.

[17] Svennungsen T, Kisdi E. Evolutionary branching of virulence in a single-infection model[J]. Journal of Theoretical Biology, 2009, 257(3): 408-418.

[18] Alizon S, Hurford A, Mideo N, et al. Virulence evolution and the trade-off hypothesis: history, current state of affairs and the future[J]. Journal of Evolutionary Biology, 2010, 22(2): 245-259.

[19] Morozov A, Best A. Predation on infected host promotes evolutionary branching of virulence and pathogens biodiversity[J]. Journal of Theoretical Biology, 2012, 307: 29-36.

[20] Kisdi E. Evolutionary branching under asymmetric competition[J]. Journal of Theoretical Biology, 1999, 197 (2): 149-162.

[21] Law R, Marrow P, Dieckmann U. On evolution under asymmetric competition[J]. Evolutionary Ecology, 1997, 11(4): 485-501.

[22] André J B, Gandon S. Vaccination, within-host dynamics, and virulence evolution[J]. Evolution, 2006, 60(1): 13-23.

[23] Frank S A. Models of parasite virulence[J]. Quarterly Review of Biology, 1996, 71(1): 37-78.

[24] Doebeli M, Dieckmann U. Evolutionary branching and sympatric speciation caused by different types of ecological interactions[J]. American Naturalist, 2000, 156(S4): 77-101.

[25] Geritz S A H, Kisdi É, Meszéna G, et al. Evolutionary singular strategies and the adaptive growth and branching of the evolutionary tree[J]. Evolutionary Ecology, 1998, 12(1): 35-57.

[26] Gyllenberg M, Parvinen K, Dieckmann U. Evolutionary suicide and evolution of dispersal in structured metapopulations[J]. Journal of Mathematical Biology, 2002, 45(2): 79-105.

[27] Marrow P, Dieckmann U, Law R. Evolutionary dynamics of predator-prey systems: an ecological perspective[J]. Journal of Mathematical Biology, 1996, 34(5/6): 556-578.

[28] Dieckmann U, Metz J A J. Surprising evolutionary prediction from enhanced ecological realism[J]. Theoretical Population Biology, 2006, 69(3): 263-281.

[29] Boldin B, Kisdi E. On the evolutionary dynamics of pathogens with direct and environmental transmission[J]. Evolution, 2012, 66(8): 2514-2527.

[30] Wilsenach J, Landi P, Hui C. Evolutionary fields can explain patterns of high dimensional complexity in ecology[J]. Physical Review E, 2017, 95(4): 042401.

[31] Su Min, Hui Cang. The effect of predation on the prevalence and aggregation of pathogens in prey[J]. Biosystems, 2011, 105(3): 300-306.

[32] Su Min, Hui Cang, Lin Zhen-shan. Effects of the transmissibility and virulence of pathogens on intraguild predation in fragmented landscapes[J]. Biosystems, 2015, 129(1): 44-49.

[33] de Leo G, Dobson A, Goodman A. Wildlife perspectives on the evolution of virulence[C]//Dieckmann U, Metz J A, Sabelis M W, et al. Adaptive dynamics of infectious diseases: in pursuit of virulence management. Cambridge: Cambridge University Press, 2002: 26-38.

[34] Su Min, Li Wen-long, Li Zi-zhen, et al. The effect of spatial heterogeneity in landscape on the host-parasite dynamics[J]. Ecological Research, 2009, 24(4): 889-896.

[35] Assan B, Nyabadza F, Landi P, et al. Modelling the transmission of Burili ulcer in fluctuating environments[J]. International Journal of Biomathematics, 2017, 100(5): 45-67.

[36] Osnas E E, Dobson A P. Evolution of virulence in heterogeneous host communities under multiple trade-offs[J]. Evolution, 2012, 66(2): 391-401.

[37] Brännström A, Loeuille N, Loreau M, et al. Emergence and maintenance of biodiversity in an evolutionary

food-web model[J]. Theoretical Ecology, 2011, 4(4): 467-478.

[38] Hui Cang, Minoarivelo H O, Nuwagaba S, et al. Adaptive diversification in coevolutionary systems[C]//Pontarotti P. Evolutionary biology: biodiversification from genotype to phenotype. Berlin: Springer International Publishing, 2015: 167-186.

[39] Minoarivelo H O, Hui Cang. Trait-mediated interaction leads to structural emergence in mutualistic networks[J]. Evolutionary Ecology, 2016, 30(1): 105-121.

[40] Hui Cang, Minoarivelo H O, Landi P. Modelling coevolution in ecological networks with adaptive dynamics [J/OL]. Mathematical Methods in the Applied Sciences. [2017-07-14]. https://onlinelibrary.wiley.com/doi/pdf/10.1002/mma.4612.

[41] Ma Zhi-hui, Wang Ting-ting, Wang Shu-fan. An eco-epidemiological model with prey refuges and a saturation incidence rate[J]. 兰州大学学报: 自然科学版, 2017, 53(6): 826-831, 836.

[42] 韩怡茹, 吴事良. 一类非自治SIRS传染病模型[J]. 兰州大学学报: 自然科学版, 2017, 53(5): 671-678.

[43] 王烈. 带有多时滞和Holling第Ⅲ类功能性反应的生态经济微分代数系统的稳定性与Hopf分支[J]. 兰州大学学报: 自然科学版, 2017, 53(5): 679-683.

[44] Garden S, Day T. Evolutionary epidemiology and the dynamics of adaption[J]. Evolution, 2010, 63(4): 826-838.

[45] van Baalen M, Sabelis M W. The dynamics of multiple infection and the evolution of virulence[J]. American Naturalist, 1995, 146(6): 881-910.

(责任编辑: 王春燕)